CLAIMS

1. Use of a multifunctional angiotensin converting enzyme (ACE) inhibitor comprising in one molecule
   i) an ACE-inhibitor component,
   ii) at least one reactive oxygen species (ROS) scavenger component, and optionally
   iii) at least one nitric oxide (NO) donor component
   in the preparation of a medicament.

2. Use according to claim 1 of a multifunctional ACE inhibitor comprising
   i) an ACE-inhibitor component,
   ii) at least one ROS-scavenger component, and
   iii) at least one nitric oxide (NO) donor component.

3. Use according to claim 1, wherein said an ACE-inhibitor component is selected from the group consisting of compounds used in medicine as ACE-inhibitors, derivatives thereof, and compounds exhibiting affinity for ACE.

4. Use according to claim 1, wherein said ROS-scavenger component comprises an antioxidant reacting with ROS selected from the group consisting of superoxide, hydroxyl radicals, peroxynitrite, and hypochlorite.

5. Use according to claim 1, wherein said NO-donor comprises a group capable of providing nitric oxide in a form selected from uncharged and charged.

6. Use according to claim 4, wherein said ROS-scavenger component comprises a substituted N-oxide free radical.

7. Use according to claim 4, wherein the N-atom of said N-oxide is a member of a 3 to 7 membered heterocyclic ring.

8. Use according to claim 5, wherein said NO donor component comprises a group selected from —ONO_2, —ONO, —SNO, and —NONOate.

18. Use according to any one of claims 13 to 16, wherein said inhibitor comprises at least one ROS scavenger component being substituted N-oxide free radical in which the N-atom of said N-oxide is a member of 3 to 7 membered heterocyclic ring.

19. Use according to any one of claims 13 to 16, wherein said inhibitor comprises at least one NO-donor component selected from—ONO_2, —ONO, —SNO, and —NONOate.

20. A multifunctional angiotensin converting enzyme (ACE) inhibitor comprising in one molecule
    i) an ACE-inhibitor component,
    ii) at least one reactive oxygen species (ROS) scavenger component, and optionally
    iii) at least one nitric oxide (NO) donor component
    for use as a medicament.

21. A method of treating or preventing a disorder selected from the group consisting of disorders in which treatment with an ACE-inhibitor is indicated, cardiovascular disorders, renal disorders, and diabetes associated disorders, in a mammal in need of said treating or preventing, comprising administering to said mammal an effective amount of a multifunctional ACE inhibitor comprising in one molecule i) an ACE inhibitor component, ii) at least one reactive oxygen species (ROS) scavenger component, and optionally iii) at least one nitric oxide (NO) donor component.

22. A method according to claim 21, wherein said disorder is selected from the group consisting of ischaemic heart disease, angina pectoris, myocardial infarction, congestive heart failure, cardiomyopathy, atherosclerosis or Reaven's Syndrome, ischaemia-reperfusion tissue injury, peripheral vascular disease, critical limb ischaemia, palpitations, arrhythmias, arterial aneurysm, microvascular diseases, hypertension selected from pulmonary-, systemic-, ocular-, obesity-, and pregnancy-induced, impotence, diabetes mellitus,

hypercholestemia, insulin-resistance and glucose intolerance in diabetes, endothelial dysfunction-induced diseases, drug or disease induced nephropathy, thyrotoxicosis, and migraine.

23. A method according to claim 21, wherein said administration or treatment is selected from the group consisting of topical, oral, and parenteral.

24. A method according to claim 21, wherein said administration or treatment is selected from the group consisting of suppository, by way of injection, and by way of infusion.

25. A method according to claim 21, wherein said multifunctional ACE inhibitor is administered by a route selected from intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, implant, inhalation spray, nasal, vaginal, rectal, sublingual, and urethral.

26. A method according to claim 21, wherein said mammal is human.

27. A multifunctional ACE inhibitor comprising
    i) an ACE-inhibitor component,
    ii) at least one ROS-scavenger component, and optionally
    iii) at least one nitric oxide (NO) donor component.

28. A multifunctional ACE inhibitor comprising
    i) an ACE-inhibitor component,
    ii) at least one ROS-scavenger component, and
    iii) at least one nitric oxide (NO) donor component.

29. A multifunctional ACE inhibitor according to claim 27, wherein said ACE-inhibitor component is selected from the group consisting of compounds used in medicine as ACE-inhibitors, derivatives thereof, and compounds exhibiting affinity for ACE.

44. A pharmaceutical composition comprising an inhibitor according to any one of claims 27 to 43, or a derivative thereof selected from the group consisting of optical isomer, solvate, and salt.

45. A pharmaceutical composition according to claim 44 further comprising a component selected from carrier, binding agent, stabilizer, adjuvant, diluent, excipient, surfactant, odorant, and a second pharmaceutically active agent.

46. A pharmaceutical composition according to claim 44, for use as a medicament for treating or preventing a disorder selected from the group consisting of disorders in which treatment with an ACE-inhibitor is indicated, cardiovascular disorders, renal disorders, and diabetes associated disorders.

47. A composition according to claim 44 for use as a medicament for treating a disorder selected from the group consisting of ischaemic heart disease, angina pectoris, myocardial infarction, congestive heart failure, cardiomyopathy, atherosclerosis or Reaven's Syndrome, ischaemia-reperfusion tissue injury, peripheral vascular disease, critical limb ischaemia, palpitations, arrhythmias, arterial aneurysm, microvascular diseases, hypertension selected from pulmonary-, systemic-, ocular-, obesity-, and pregnancy-induced, impotence, diabetes mellitus, hypercholestemia, insulin-resistance and glucose intolerance in diabetes, endothelial dysfunction-induced diseases, drug or disease induced nephropathy, thyrotoxicosis, and migraine.

48. A kit for administering a multifunctional ACE inhibitor comprising
    i) a dosage amount of at least one compound having ACE inhibitor activity and ROS-scavenging activity,
    ii) instructions for use; and
    iii) optionally means for the delivery of said compound.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 16959/WO/03	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IL 03/01006	International filing date *(day/month/year)* 27.11.2003	Priority date *(day/month/year)* 29.11.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/385		
Applicant YISSUM RESEARCH DEVELOPMENT COMPANY OF THE...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.06.2004	02.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Büttner, U Telephone No. +49 89 2399-7841

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IL 03/01006

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-72	as originally filed

Claims, Numbers

9-17, 30-43	as originally filed
1-8, 18-29, 44-48	filed with telefax on 10.02.2005

Drawings, Sheets

1/2-2/2	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

   see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 21-26 with respect to Industrial Applicability

   because:

   ☒ the said international application, or the said claims Nos. 21-26 with respect to Industrial Applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-11, 20-35, 44-48 (all in part); 12, 36 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7,33
	No:	Claims	1-6, 8-12, 20-32, 34-36, 44-48
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12, 20-36, 44-48
Industrial applicability (IA)	Yes:	Claims	1-20,27-48
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item I

Basis of the report

The amendments filed with the letter dated 10.02.05 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT.

The amendments concerned are the following:

The applicant did not provide any basis for the introduction of the disclaimer the "ROS scavenger component is not identical with said ACE-inhibitor component" and the "NO-donor component is not identical with said ROS-scavenger component", nor is the IPEA able to identify any basis.

A disclaimer may be allowable in order to restore novelty by delimiting a claim against an accidental anticipation; an anticipation is accidental if it is so unrelated to and remote from the claimed invention that the person skilled in the art would never have taken it into consideration when making the invention.

The cited prior art however relates to the same matter and is therefore highly relevant. Therefore the cited prior art cannot be regarded as being accidental.

Preliminary examination is carried out on claims as originally filed.

Re item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 21-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The subject-matter of the present application is not unitary in the sense of rule 13.1 PCT for the following reasons:

the problem posed in the present application was :

the treatment of conditions as defined in claim 10

Claim 1 suggests the use of compounds comprising an ACE inhibitor component and ROS scavenger component.

Documents D7-D9 disclose that the examined ACE inhibitors such as enalapril or captopril show an antioxidant effect (see below).

Therefore compounds comprising an ACE inhibitor component and ROS scavenger component and their use in the defined conditions are not new.

Claim 2 suggests the use of compounds comprising an ACE inhibitor component and ROS scavenger component and a NO donor component.

Documents D1-D6 disclose ACE inhibitors, for which an antioxidant activity is known (see e.g. D7-D9) or which at least comprise an antioxidant component as defined in the present application (p. 19, paragraph 2 and 3), which additionally comprise a NO donor component for the treatment of conditions as defined in claim 10.

Therefore compounds comprising an ACE inhibitor component, a ROS scavenger component and a NO donor component and their use in the defined conditions are not new.

Therefore the functional features of claims 1 and 2 cannot account any longer as NOVEL common inventive concept linking the various structures listed in the application.

Moreover the compounds disclosed in the above mentioned prior art (e.g. captopril) fall within the basic structure of general formulae I-II (R1 =OH, R^4 and R^5 form a ring) of claims 13-14, which only differ from the mentioned prior art in R3 (for claims 13 and 14) .
Therefore the basic structure of formulae I-II is not novel and cannot account any longer as novel common inventive concept linking the various radicals R3 as defined in claims 13 or 14.
In the same way the basic formulae of claims 13 and 14 cannot account any longer as novel common inventive concept linking formulae (I and II) and III as defined in claim 15.

Additionally the compounds disclosed in the above mentioned prior art (e.g. enalapril or quinalapril) fall within the basic structure of general formula III of claim 15, which only differ from the mentioned prior art in R6 (for claim 15) . Therefore the basic structure of formula III is not novel and cannot account any longer as novel common inventive concept linking the various radicals R6 as defined in claim 15.

Moreover a N-oxide being a member of 3 to 7 membered heterocyclic ring acting as ROS scavenger component (even in combination with a NO donating group) for treating vascular diseases is known from D10. Therefore it could not account any longer as novel inventive concept linking the various heterocyclic rings being a N-oxide free radical.

Therefore 4 different alternatives were identified in the present application, wherein the IPEA was unable to acknowledge any common NOVEL chemical structure:

1.) Claims 1-11, 20-35, 44-48 (all in part); 12, 36
use of compounds comprising an ACE inhibitor component derived from a commercially available ACE inhibitor as defined in claim 12 a ROS scavenger component and optionally a NO donor component for the treatment of conditions as defined in claim 10.

2.) Claims 1-11, 18-35, 44-48 (all in part); 13, 14, 37-39
use of compounds comprising an ACE inhibitor component comprising a heterocycle as defined in claims 13 and 14 for the treatment of conditions as defined in claim 10.

3.) Claims 1-11, 18-35, 44-48 (all in part); 15, 40, 41
use of compounds comprising an ACE inhibitor component comprising a heterocycle as defined in claims 15 for the treatment of conditions as defined in claim 10.

4.) Claims 1-11,18-35, 44-48 (all in part); 16, 17, 42, 43
use of compounds comprising an ACE inhibitor component according to formula IV as defined in claim 17 (compounds falling under the scope of claim 12 being excluded) for the treatment of conditions as defined in claim 10.

Moreover the combination of the functional features as defined in claim 1 and 2 would not involve an inventive step (see D1-D5)

Moreover, the IPEA is unable to identify any NOVEL common inventive concept linking the various subject-matters 1 to 4.

Accordingly, the present application is not unitary and contains the four different subject-matters identified above. The examination has therefore been restricted to the first invention identified.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.) Reference is made to the following documents:

D1: WO 02/34303 A (UNIV BOSTON ;VITA JOSEPH A (US); WORCEL MANUEL (US); LOSCALZO JOSE) 2 May 2002 (2002-05-02)

D2: WO 98/21193 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 22 May 1998 (1998-05-22)

D3: WO 00/61541 A (NICOX SA ;DEL SOLDATO PIERO (IT)) 19 October 2000 (2000-10-19)

D4: US-A-5 025 001 (LOSCALZO JOSEPH ET AL) 18 June 1991 (1991-06-18)

D5: JIA LEE ET AL: 'The effects of S-nitrosocaptopril on renal filtration and blood pressure in rats' EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 354, no. 1, 31 July 1998 (1998-07-31), pages 33-41, XP002277634 ISSN: 0014-2999

D6: IWANAGA YOSHITAKA ET AL: 'A nitric oxide-releasing derivative of enalapril, NCX 899, prevents progressive LV dysfunction and improves remodeling in cardiomyopathic hamsters with heart failure.' CIRCULATION, vol. 106, no. 19 Supplement, 5 November 2002 (2002-11-05), pages II-510, XP009029725 Abstracts from Scientific Sessions;Chicago, IL, USA; November 17-20, 2002

ISSN: 0009-7322 (ISSN print)

D7: VAN DER GIET M ET AL: 'Captopril and quinapril reduce reactive oxygen species.' EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, vol. 32, no. 10, October 2002 (2002-10), pages 732-737, XP002277635 ISSN: 0014-2972

D8: DJORDJEVIC V B ET AL: 'CHANGES OF LIPID PEROXIDES AND ANTIOXIDATIVE FACTORS LEVELS IN BLOOD OF PATIENTS TREATED WITH ACE INHIBITORS' CLINICAL NEPHROLOGY, DUSTRI VERLAG, NUENCHEN-DEISENHOFEN, DE, vol. 47, no. 4, April 1997 (1997-04), pages 243-247, XP001104974 ISSN: 0301-0430

D9: ARUOMA O I ET AL: 'EVALUATION OF THE ABILITY OF THE ANGIOTENSIN-CONVERTING ENZYME INHIBITOR CAPTOPRIL TO SCAVENGE REACTIVE OXYGEN SPECIES' CHEMICO-BIOLOGICAL INTERACTIONS, vol. 77, no. 3, 1991, pages 303-314, XP002277636 ISSN: 0009-2797

D10: WO 99/37616 A (AENGGAARD ERIK EMIL ;HAJ YEHIA ABDULLAH IBRAHIM (IL)) 29 July 1999 (1999-07-29)

2.) The present application does not meet the requirements of Article 52(1) EPC, because the subject-matter of claims 1-6, 8-12, 20-32, 34-36, 44-48 (and 19,42 43) is not new in the sense of Article 54(1) and (2) EPC.

Document D7 discloses that ACE inhibitors quinapril and captopril inhibit the production of ROS. Results are also obtained in vivo. Therefore the subject matter of claims 1, 3, 4, 9-12, 21-27, 29-31, 36, 42-48 is not new.

Document D8 discloses that captopril and enalapril act as ROS scavenger. Therefore the subject matter of claims 1, 3, 4, 9-12, 21-27, 29-31, 36, 42-48 is not new.

Document D9 discloses that captopril reacts fast with hydroxyl radicals and hypochlorite. Therefore the subject matter of claims 1, 3, 4, 9-12, 21-27, 29-31, 36, 44-48 is not new.

It has to be noted that the term "ROS scavenger" is in not limited to superoxide

scavengers in vivo (see p. 18 l. 12-19 of the present application).
Moreover, even in the absence of any prior art indicating a ROS scavenging affect of quinabril, captopril, or enalapril, said ACE-inhibitors would have a ROS scavenging activity, since they possess ROS scavenger moieties such as defined on p. 19 of the present application. Therefore they inherently have a ROS scavenging component.

Document D1 discloses nitrosated ACE inhibitors such as nitroso captopril for the treatment of cardiovascular diseases. Therefore the subject matter of claims 1-6, 8-12, 20-32, 34-36, 44-48 is not new.

Document D2 discloses that NO- ACE inhibitors such as NO-enalapril have an antihypertensive activity. Therefore the subject matter of claims 1-6, 8-12, 19-32, 34-36, 42-48 is not new.

Document D3 discloses nitrosated ACE inhibitors for the treatment of cardiovascular diseases. Therefore the subject matter of claims 1-6, 8-12, 20-32, 34-36, 44-48 is not new.

Document D4 discloses nitroso derivatives of ACE inhibitors such as nitroso captopril for the treatment of diseases such as myocardial infarction or hypertension. Therefore the subject matter of claims 1-6, 8-12, 20-32, 34-36, 44-48 is not new.

Document D5 discloses that S-nitrosocaptopril possessing ACE inhibiting and NO donor capacities significantly decreases blood pressure. Therefore the subject matter of claims 1-6, 8-12, 20-32, 34-36, 44-48 is not new.

Document D6 discloses that ncx 899 a nitric oxide releasing derivative of enalapril prevented systolic and diastolic dysfunction. Therefore the subject matter of claims 1-6, 8-12, 19-32, 34-36, 42-48 is not new.

3.) The present application does not meet the requirements of Article 52(1) EPC, because the subject-matter of claims 7, 33 does not involve an inventive step in the sense of Article 56 EPC.

Document D10 discloses N-oxide being a member of 3 to 7 membered heterocyclic ring acting as ROS scavenger component (even in combination with a NO donating group) for treating vascular diseases. Therefore the use of a N-oxide free radical comprising ring does not involve an inventive step.

4.) For the assessment of the present claims 21-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.